

### CLAIMS

What is claimed is:

1. A crystalline form of azithromycin selected from the group consisting of forms D, E, substantially pure F, G, J, M substantially in the absence of azithromycin dihydrate,  
5 N, O, P, Q, and R.
2. A crystalline form of azithromycin according to claim 1 wherein said form is form D.
3. A crystalline form according to claim 2 wherein said form is characterized as containing 2-6% water and 3-12% cyclohexane by weight in a powder sample.
4. A pharmaceutical composition comprising a crystalline form of azithromycin according  
10 to claim 2 and a pharmaceutically acceptable excipient.
5. A crystalline form of azithromycin according to claim 2 wherein said form is further characterized as having a <sup>13</sup>C solid state NMR spectrum comprising a plurality of peaks with chemical shifts of about 178.1 ppm, 103.9 ppm, 95.1 ppm, 84.2 ppm, 10.6 ppm, 9.0 ppm and 8.6 ppm.
- 15 6. A crystalline form of azithromycin according to claim 1 wherein said form is form E.
7. A pharmaceutical composition comprising a crystalline form of azithromycin according to claim 6 and a pharmaceutically acceptable excipient.
8. A crystalline form of azithromycin according to claim 1 wherein said form is substantially pure form F.
- 20 9. A crystalline form according to claim 8 wherein said form is characterized as containing 2-5% water and 1-5% ethanol by weight in a powder sample.
10. A crystalline form of azithromycin according to claim 8 wherein said form is further characterized as having a <sup>13</sup>C solid state NMR spectrum comprising a plurality of  
25 peaks with chemical shifts of about 179.5 ppm, 178.6 ppm, 58.0 ppm, 17.2 ppm, 10.1 ppm 9.8 ppm, 9.3 ppm, 7.9 ppm and 6.6 ppm.
11. A crystalline form of azithromycin according to claim 8 wherein said azithromycin comprises more than 80% by weight of form F azithromycin.
12. A crystalline form of azithromycin according to claim 8 wherein said azithromycin comprises 81% or more by weight of form F azithromycin.

13. A crystalline form of azithromycin according to claim 8 wherein said azithromycin comprises 82% or more by weight of form F azithromycin.
14. A crystalline form of azithromycin according to claim 8 wherein said azithromycin comprises 83% or more by weight of form F azithromycin.
- 5 15. A crystalline form of azithromycin according to claim 8 wherein said azithromycin comprises 84% or more by weight of form F azithromycin.
16. A crystalline form of azithromycin according to claim 8 wherein said azithromycin comprises 85% or more by weight of form F azithromycin.
- 10 17. A crystalline form of azithromycin according to claim 8 wherein said azithromycin comprises 86% or more by weight of form F azithromycin.
18. A crystalline form of azithromycin according to claim 8 wherein said azithromycin comprises 87% or more by weight of form F azithromycin.
19. A crystalline form of azithromycin according to claim 8 wherein said azithromycin comprises 88% or more by weight of form F azithromycin.
- 15 20. A crystalline form of azithromycin according to claim 8 wherein said azithromycin comprises 89% or more by weight of form F azithromycin.
21. A crystalline form of azithromycin according to claim 8 wherein said azithromycin comprises 90% or more by weight of form F azithromycin.
- 20 22. A crystalline form of azithromycin according to claim 8 wherein said azithromycin comprises 91% or more by weight of form F azithromycin.
23. A crystalline form of azithromycin according to claim 8 wherein said azithromycin comprises 92% or more by weight of form F azithromycin.
24. A crystalline form of azithromycin according to claim 8 wherein said azithromycin comprises 93% or more by weight of form F azithromycin.
- 25 25. A crystalline form of azithromycin according to claim 8 wherein said azithromycin comprises 94% or more by weight of form F azithromycin.
26. A crystalline form of azithromycin according to claim 8 wherein said azithromycin comprises 95% or more by weight of form F azithromycin.

27. A crystalline form of azithromycin according to claim 8 wherein said azithromycin comprises 96% or more by weight of form F azithromycin.
28. A crystalline form of azithromycin according to claim 8 wherein said azithromycin comprises 97% or more by weight of form F azithromycin.
- 5 29. A crystalline form of azithromycin according to claim 8 wherein said azithromycin comprises 98% or more by weight of form F azithromycin.
30. A crystalline form of azithromycin according to claim 8 wherein said azithromycin comprises 99% or more by weight of form F azithromycin.
- 10 31. A pharmaceutical composition comprising a crystalline form of azithromycin as in claim 8 or in one of claims 11-30 and a pharmaceutically acceptable excipient
32. A crystalline form of azithromycin according to claim 1 wherein said form is form G.
33. A crystalline form of azithromycin according to claim 1 wherein said form is substantially pure form G.
- 15 34. A crystalline form according to claim 32 or claim 33 wherein said form is characterized as containing 2-6% water and less than 1% organic solvent by weight in a powder sample.
- 20 35. A crystalline form of azithromycin according to claim 32 or claim 33 wherein said form is further characterized as having a <sup>13</sup>C solid state NMR spectrum comprising a plurality of peaks with chemical shifts of about 179.5 ppm, 10.4 ppm, 9.9 ppm, 9.3 ppm, 7.6 ppm and 6.5 ppm.
36. A crystalline form of azithromycin according to claim 32 wherein said azithromycin comprises more than 50% by weight of form G azithromycin.
37. A crystalline form of azithromycin according to claim 32 wherein said azithromycin comprises 55% or more by weight of form G azithromycin.
- 25 38. A crystalline form of azithromycin according to claim 32 wherein said azithromycin comprises 60% or more by weight of form G azithromycin.
39. A crystalline form of azithromycin according to claim 32 wherein said azithromycin comprises 65% or more by weight of form G azithromycin.

40. A crystalline form of azithromycin according to claim 32 wherein said azithromycin comprises 70% or more by weight of form G azithromycin.
41. A crystalline form of azithromycin according to claim 32 wherein said azithromycin comprises 75% or more by weight of form G azithromycin.
- 5 42. A crystalline form of azithromycin according to claim 32 wherein said azithromycin comprises 80% or more by weight of form G azithromycin.
43. A crystalline form of azithromycin according to claim 32 wherein said azithromycin comprises 85% or more by weight of form G azithromycin.
44. A crystalline form of azithromycin according to claim 32 wherein said azithromycin  
10 comprises 90% or more by weight of form G azithromycin.
45. A crystalline form of azithromycin according to claim 32 wherein said azithromycin comprises 91% or more by weight of form G azithromycin.
46. A crystalline form of azithromycin according to claim 32 wherein said azithromycin comprises 92% or more by weight of form G azithromycin.
- 15 47. A crystalline form of azithromycin according to claim 32 wherein said azithromycin comprises 93% or more by weight of form G azithromycin.
48. A crystalline form of azithromycin according to claim 32 wherein said azithromycin comprises 94% or more by weight of form G azithromycin.
49. A crystalline form of azithromycin according to claim 32 wherein said azithromycin  
20 comprises 95% or more by weight of form G azithromycin.
50. A crystalline form of azithromycin according to claim 32 wherein said azithromycin comprises 96% or more by weight of form G azithromycin.
51. A crystalline form of azithromycin according to claim 32 wherein said azithromycin comprises 97% or more by weight of form G azithromycin.
- 25 52. A crystalline form of azithromycin according to claim 32 wherein said azithromycin comprises 98% or more by weight of form G azithromycin.
53. A crystalline form of azithromycin according to claim 32 wherein said azithromycin comprises 99% or more by weight of form G azithromycin.

54. A pharmaceutical composition comprising a crystalline form of azithromycin according to claim 32 or claim 33 or one of claims 36-53 and a pharmaceutically acceptable excipient
55. A crystalline form according to claim 1 wherein said form is form H.
- 5 56. A crystalline form of azithromycin according to claim 55 wherein said form is further characterized as having a <sup>13</sup>C solid state NMR spectrum comprising a plurality of peaks with chemical shifts of about 179.5 ppm, 178.7 ppm, 9.9 ppm, 9.1 ppm, 7.9 ppm and 7.0 ppm.
- 10 57. A pharmaceutical composition comprising a crystalline form of azithromycin according to claim 55 and a pharmaceutically acceptable excipient
58. A crystalline form according to claim 1 wherein said form is form J.
59. A crystalline form according to claim 58 wherein said form is characterized as containing 2-5% water and 1-5% n-propanol by weight in a powder sample.
- 15 60. A crystalline form according to claim 58 wherein said form is further characterized as having a <sup>13</sup>C solid state NMR spectrum comprising a plurality of peaks with chemical shifts of about 179.6 ppm, 178.4 ppm, 25.2 ppm, 11.5 ppm, 10.0 ppm, 9.3 ppm, 8.1 ppm and 6.8 ppm.
61. A pharmaceutical composition comprising a crystalline form of azithromycin according to claim 58 and a pharmaceutically acceptable excipient.
- 20 62. A crystalline form according to claim 1 wherein said form is form M substantially in the absence of azithromycin dihydrate.
63. A crystalline form according to claim 62 wherein said form is characterized as containing 2-5% water and 1-7% 2-propanol by weight in a powder sample.
- 25 64. A crystalline form according to claim 62 wherein said form is further characterized as having a <sup>13</sup>C solid state NMR spectrum comprising a plurality of peaks with chemical shifts of about 179.6 ppm, 41.9, 26.0 ppm, 16.3 ppm, 10.3 ppm, 9.6 ppm, 9.3 ppm, 7.7 ppm and 7.1 ppm.
65. A crystalline form of azithromycin according to claim 62 wherein said azithromycin comprises less than 5% by weight of azithromycin dihydrate.

66. A crystalline form of azithromycin according to claim 62 wherein said azithromycin comprises less than 4% by weight of azithromycin dihydrate.
67. A crystalline form of azithromycin according to claim 62 wherein said azithromycin comprises less than 3% by weight of azithromycin dihydrate.
- 5 68. A crystalline form of azithromycin according to claim 62 wherein said azithromycin comprises less than 2% by weight of azithromycin dihydrate.
69. A crystalline form of azithromycin according to claim 62 wherein said azithromycin comprises less than 1% by weight of azithromycin dihydrate.
- 10 70. A pharmaceutical composition comprising a crystalline form of azithromycin according to one of claims 62-69 and a pharmaceutically acceptable excipient.
71. A crystalline form according to claim 1 wherein said form is form N.
72. A crystalline form according to claim 71 wherein said form is characterized as containing 1-5% water and 2-5% organic solvent by weight in a powder sample.
- 15 73. A crystalline form according to claim 71 wherein said form is further characterized as having a <sup>13</sup>C solid state NMR spectrum comprising a plurality of peaks with chemical shifts of about 179.6 ppm, 178.7 ppm, 58.1 ppm, 26.0 ppm, 9.9 ppm, 9.4 ppm, 7.9 ppm, and 6.6 ppm.
74. A pharmaceutical composition comprising a crystalline form of azithromycin according to one of claims 71-73 and a pharmaceutically acceptable excipient.
- 20 75. A crystalline form according to claim 1 wherein said form is form O.
76. A pharmaceutical composition comprising a crystalline form of azithromycin according to claim 75 and a pharmaceutically acceptable excipient.
77. A crystalline form according to claim 1 wherein said form is form P.
- 25 78. A pharmaceutical composition comprising a crystalline form of azithromycin according to claim 87 and a pharmaceutically acceptable excipient.
79. A crystalline form according to claim 1 wherein said form is form Q.
80. A pharmaceutical composition comprising a crystalline form of azithromycin according to claim 79 and a pharmaceutically acceptable excipient.

81. A crystalline form according to claim 1 wherein said form is form R.
82. A crystalline form according to claim 81 wherein said form is further characterized as having a  $^{13}\text{C}$  solid state NMR spectrum having a plurality of peaks with chemical shifts of about 177.9 ppm, 95.3 ppm, 10.3 ppm, 9.6 ppm, 8.9 ppm, and 8.6 ppm.
- 5 83. A pharmaceutical composition comprising a crystalline form of azithromycin according to claim 81 or 82 and a pharmaceutically acceptable excipient.
84. An azithromycin mixture comprising azithromycin dihydrate and one or more hydrate/solvates of azithromycin or azithromycin sesquhydrate.
- 10 85. An azithromycin mixture according to claim 84 wherein the hydrate/solvate contains a solvent selected from the group consisting of ethanol, 2-propanol, n-propanol, formic acid, butanol, pentanol, tetrahydrofuran, propylene glycol, acetone, cyclohexane, and acetonitrile
- 15 86. An azithromycin mixture comprising azithromycin dihydrate and one or more forms of azithromycin selected from the group consisting of form D, form F, form G, form H, form J, form M, form O, form Q and form R.
87. An azithromycin mixture according to claim 86 comprising form A and form F.
88. An azithromycin mixture according to claim 86 comprising form A and form G.
89. An azithromycin mixture according to claim 86 comprising form A and form H.
90. An azithromycin mixture according to claim 86 comprising form A and form J.
- 20 91. An azithromycin mixture according to claim 86 comprising form A and form M.
92. An azithromycin mixture according to claim 86 comprising form A and form F and form G.
93. An azithromycin mixture according to claim 86 comprising form A and form G and form M.
- 25 94. A family of azithromycin crystalline forms wherein said family is Family II.
95. The family of claim 64 wherein said family is characterized as belonging to an orthorhombic  $\text{P}2_12_12_1$  space group with cell dimensions of  $a = 8.8 \pm 0.4 \text{ \AA}$ ,  $b = 12.3 \pm 0.5 \text{ \AA}$  and  $c = 45 \pm 0.5 \text{ \AA}$ .

96. A method of preparing the crystalline form of claim 2 comprising the step of slurring azithromycin with cyclohexane and isolating crystalline azithromycin.
97. A method of preparing the crystalline form of claim 8 comprising the steps of dissolving azithromycin in ethanol to form an ethanol solution, cooling the ethanol solution to below 20°C, precipitating azithromycin crystals and isolating the crystals.
98. A method according to claim 97 wherein the ethanol solution is cooled to 15°C or below.
99. A method according to claim 97 wherein the ethanol solution is cooled to 10°C or below.
100. A method according to claim 97 wherein the ethanol solution is cooled to 5°C or below.
101. A method as in one of claims 97-100 further comprising the step of adding water to the ethanol solution after the ethanol solution has been cooled.
102. A method according to claim 101 further comprising the step of cooling the water prior to adding the water to the ethanol solution.
103. A method according to claim 102 wherein the water is cooled to below 20°C.
104. A method according to claim 102 wherein the water is cooled to 15°C or below.
105. A method according to claim 102 wherein the water is cooled to 10°C or below.
106. A method according to claim 102 wherein the water is cooled to 5°C or below.
107. A method according to one of claims 97 to 100 further comprising the step of seeding the cooled ethanol solution with crystals of form F azithromycin.
108. A method of preparing the crystalline form of claim 32 comprising the steps of dissolving azithromycin in a 1:1 mixture of water and a solvent that is a member selected from the group consisting of methanol, acetone, acetonitrile, adding water to the mixture, precipitating azithromycin crystals and isolating the crystals.
109. A method of preparing the crystalline form of claim 58 comprising the steps of dissolving azithromycin in n-propanol, adding water, precipitating azithromycin crystals and isolating the crystals.



110. A method of preparing the crystalline form of claim 62 comprising the steps of dissolving azithromycin with isopropanol to form an isopropanol solution, cooling the isopropanol solution to below 15°C, adding water after the isopropanol solution has been cooled, precipitating azithromycin crystals and isolating the crystals.
- 5 111. A method according to claim 110 wherein the isopropanol solution is cooled to 10°C or below.
112. A method according to claim 110 wherein the isopropanol solution is cooled to 5°C or below.
- 10 113. A method according to one of claims 110 to 112 wherein the water is cooled prior to adding the water to the isopropanol solution.
114. A method according to claim 113 wherein the water is cooled to 20°C or below.
115. A method according to claim 113 wherein the water is cooled to 15°C or below.
116. A method according to claim 113 wherein the water is cooled to 10°C or below.
117. A method according to claim 113 wherein the water is cooled to 5°C or below.
- 15 118. A method according to claim 110 wherein the crystals are isolated within 5 hours of precipitation.
119. A method according to claim 110 wherein the crystals are isolated within 3 hours of precipitation.
- 20 120. A method according to claim 110 wherein the crystals are isolated within 1 hour of precipitation.
121. A method according to claim 110 wherein the crystals are isolated within 30 minutes of precipitation.
- 25 122. A method according to one of claims claim 110 to 112 further comprising the step of seeding the cooled isopropanol solution with crystals of the crystalline form of claim 62.
123. A method of treating a bacterial infection or a protozoa infection in a mammal, fish, or bird which comprises administering to said mammal, fish or bird a therapeutically

effective amount of crystalline azithromycin according to claim 1 or an azithromycin mixture according to claim 86.